A. The Invention

The present invention relates to an inactivated virus particle, as a reinforced immunogen, prepared from a culture of cells infected with virus belonging to a group of Japanese encephalitis viruses. The inactivated virus particle is prepared by a process comprising a step of inactivation followed by a step of purification solely by physical means. The inactivated virus particle when prepared by this process achieves a neutralizing antibody titer of the anti-serum obtained by immunization with the virus particles is about twice to about 10 times the neutralizing antibody titer of the anti-serum obtained by immunization with inactivated virus particles prepared from virus cultured in mouse brain.

Virus particles prepared by the process described, where (i) the step of inactivation precedes the step of purification and (ii) purification is solely by physical means, have an unaltered surface that preserves the correct steric conformation for presentation of the antigen to antibodies, leading to the high neutralizing antibody titer.

B. The Cited Art

DING ET AL. teach the production of purified Japanese encephalitis vaccine from Vero cells. The virus of Ding *et al* was inactivated, concentrated, treated with protamine sulfate, and purified.

C. Analysis

In maintaining the rejection over Ding *et al.*, the Examiner notes that the claims are drawn to a product of an inactivated virus particle that elicits high titers of neutralizing antibodies, and that the process by which the product is formed is not given patentable weight. Thus, Applicants' arguments that the present product is patentable over the cited art since it is prepared using "purification solely by physical means" were found unpersuasive. (Office Action dated December 30, 2002, page 2, final paragraph).

According to the MPEP §2113,

> "once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product." (citing *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir 1983)).

Viral particles prepared by the claimed inactivation/purification process have a viral surface that is unchanged, allowing correct steric conformation for antibody presentation. Therefore, when immunized with the virus particle of the present invention, a high titer of neutralizing antibody can be obtained due to superior antigen presentation. In contrast, virus particles purified and inactivated by prior art methods have a smooth surface that does not enable a high titer of neutralizing antibody.

Evidence of the unchanged virus particle surface for particles prepared by the inactivation/physical purification process recited in claim 1, and evidence that virus particle surfaces prepared by prior art methods are changed, is provided in Fig. 1 of the specification. In Fig. 1A, an electron photomicrograph of a virus particle prepared by the present process of inactivation followed by physical purification is shown. As seen, the surface of the envelope layer is rough or fuzzy (page 8, lines 3-6; page 5, lines 27-30). Fig. 1B is an electron photomicrograph of a virus particle prepared by prior art, commercial methods where the virus is purified and then inactivated (page 5, lines 27-30; page 7, lines 1-4). As seen in Fig. 1B, the surface of these particles is smooth (page 8, lines 3-5).

As shown by the data presented in Example 4 of the specification (page 24, beginning at line 22), virus particles prepared by the process recited in claim 1 can maintain higher immunogenicity or antigenicity, as compared with particles prepared by the prior art methods of purification followed by inactivation.

The data presented by Applicants in Fig. 1 of the specification and in Example 4 establishes an unobvious difference between the claimed product and the prior art product. Thus, Applicants submit that their burden under MPEP §2113 to come

forward with evidence establishing an unobvious difference between the claimed product and the prior art product has been met.

Returning now to the teaching of Ding *et al.*, Applicants note that Ding *et al.* teach a virus particle prepared by chemical purification followed by inactivation. This process of preparation will result in a virus particle with a smooth surface, as shown in Fig. 1B of Applicants' specification. The smooth surface is indicative that the particle has an altered steric conformation for antibody presentation, and results in lower antibody titers, as established by Example 4 of applicants' specification. Thus, the particles of Ding *et al.* are different from the claimed particles.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

II. Rejections under 35 U.S.C. §103

Claims 1-3, 5, 7, 9, 10, 13, and 15-18 were rejected under 35 U.S.C. §103 as allegedly obvious over Ding *et al.* or Huiying et al. (*Virologica Sinica*, 13:3:213 (1998)) in view of Liau *et al.* (U.S. Patent No. 6,207,439).

This rejection is respectfully traversed for the following reasons.

A. The Invention

The present invention is described above.

B. The Cited Art

DING ET AL. is described above.

HUIYING *ET AL.* relates to a method for large scale purification of Japanese Encephalitis (JE) vaccine in vero cells by (1) concentrating by ultrafiltration; (2) precipitating with protamine sulfate; and then (3) purifying by zonal centrifugation at non-continuous sucrose gradients. Huiying *et al.* do not specify how or at what point in the process inactivation is achieved.

LIAU *ET AL.* disclose a process for large-scale purification of living Japanese encephalitis virus from JEV-infected mouse brains and cell cultures. The virus is purified by the steps of microfiltration, ultrafiltration, or gel filtration and then inactivation with an inactivating agent such as formalin or binary ethyleneimide (see Table 4, Col. 9).

C. Analysis

1. Analysis of Examiner's Product-by-Process Comments

The Examiner has maintained the present rejection on the grounds noted above with respect to the rejection under 35 U.S.C. §102; that the claims are drawn to a product of an inactivated virus particle that elicits high titers of neutralizing antibodies, and that the process by which the product is formed is not given patentable weight.

The legal standard provided in M.P.E.P. §2113 and set forth above is applicable to the rejection under 35 U.S.C. §103. That is, once the examiner provides a showing that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product.

Applicants have met this burden by showing, as discussed above, that virus particles prepared by the claimed inactivation/physical purification process retain a rough or fuzzy surface (Fig. 1A of applicants' application) that permits correct steric conformation for presentation to an antibody, thus achieving a high antibody titer. In contrast, virus particles prepared by methods set forth in the cited documents where a purification (chemical or physical) step is followed by inactivation have a smooth surface (Fig. 1B of applicants' application). These particles result in a lower antibody titer, as described in Example 4 of applicants' specification.

2. Analysis of the Rejection based on the Cited Documents

Turning now to an analysis of the combined teachings of the cited documents, the Examiner has rejected the claims based on a combination of Ding *et al.* or Huiying *et al.* in view of Liau *et al.* The Examiner's rational for the rejection, provided in the June 13, 2002 Office action, is that "one would be motivated to modify Huiying *et al.* with the method steps of Ding *et al.* because Ding *et al.* teaches an inactivated virus." (Office action dated June 13, 2002, page 3). The rational is based on modification of Huiying *et al.* in view of Ding *et al.*, rather than modification of one of the primary references (Ding *et al.* and Huiying *et al.*) in view of the secondary reference of Liau *et al.* Thus, there is some uncertainty on exactly how the Examiner is combining the documents to arrive at the claimed invention, so Applicants will address all possible combinations to show that the claimed invention is not suggested by any combination of the cited art.

According to the MPEP §2143.03, "all claim limitations must be taught or suggested by the prior art. All words in a claim must be considered in judging the patentability of that claim against the prior art." As noted above, the present invention related to inactivated viral particles prepared by a process of inactivation followed by physical purification. Claim 1 includes the limitation that "a neutralizing antibody titer of the anti-serum obtained by immunization with the virus particles is about twice to about 10 times the neutralizing antibody titer of the anti-serum obtained by immunization with inactivated virus particles prepared from virus cultured in mouse brain."

Applicants submit that none of the references alone or in combination show or suggest that viral particles prepared by the inactivation/physical purification process of claim 1 would achieve the claimed high neutralizing antibody titer.

Ding *et al.* teach viral particle preparation by inactivating the virus and then chemically purifying the particles. Huiying *et al.* disclose viral particle preparation by physical purification; and there is no mention of how the viral particles are inactivated. Even if the two methodologies were combined to arrive at an inactivation process followed there is no suggestion that a unexpectedly high neutralizing antibody titer

would be obtained. "To establish...obviousness.....the prior art references (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

Similarly, modification of either Ding *et al.* or Huiying *et al.* with Liau *et al.* fails to arrive at either (1) a process of inactivation followed by physical purification in order to obtain viral particles having the claimed antibody titer level or (2) a suggestion that a high antibody titer would be achieved.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

Conclusion

In view of the foregoing, Applicants submit that the claims pending in the application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,

Jacqueline F. Mahoney

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Jacqueline F. Mahoney
Registration No. 48,390

Correspondence Address:
Customer No. 22918
Phone: (650) 838-4300